only 15 percent to 20 percent of cases being fully responsive to ^{60}cobalt radiotherapy in doses of 4,000 to 5,000 rads. However, children appear to be considerably more radiosensitive than adults and, as recently reported, as many as 80 percent can be effectively treated with radiation alone. While the lag period for full benefit may be as long as 18 months in some cases, the procedure is essentially free of morbidity, no hormone replacement is required and pituitary function has remained intact after prolonged follow-up. Based upon these encouraging results, cobalt radiotherapy can be expected to become the preferred initial treatment for pituitary Cushing syndrome in patients under 20 years of age.

Clinical trials of selected drugs have not as yet produced an agent which can be considered as sole definitive treatment. Mitotane, an adrenocorticolytic drug, has proved to be a useful adjunct for short-term improvement of patients who are incompletely treated or who are awaiting the full effects of radiation. An entirely novel, recent approach has been the introduction of two agents believed to alter brain neurotransmitter regulation of pituitary ACTH. Both cyproheptadine, a serotonin antagonist, and bromocryptine, a dopamine agonist, can ameliorate clinical features and reduce cortisol production. Careful studies of cyproheptadine indicate that not all patients are responsive and, when therapy is effective, relapse promptly follows discontinuation of the drug. However, the minimal side effects and possibility of spontaneous remissions with more prolonged treatment make these agents attractive for continuing clinical evaluation.

The single most impressive advance in management of pituitary Cushing syndrome has come with refinements in surgical procedures to the pituitary gland, now emerging as the treatment of choice in adults. This is due, in part, to improvements in radiologic diagnosis, particularly tomography, which has enabled the detection of pituitary microadenomas in more than 50 percent of patients, compared with the 5 percent in whom diagnosis is possible using conventional x-ray studies of the skull. These small tumors can now be viewed directly and resected, leaving the rest of the pituitary intact, using microdissection techniques made possible by the coupling of transsphenoidal surgical procedures with newer surgical microscopes. Two recent reports confirm 90 to 95 percent remission rates following removal of microadenomas and, equally impressive, this has been achieved without operative mortality and in almost all cases without permanent pituitary failure. It is noteworthy that whereas surgical operation in one series was used only in patients in whom abnormalities were shown on radiographs, Wilson and his group successfully operated on 16 of 17 patients despite normal findings on tomograms in 40 percent of them. This has led the latter group and others to advocate surgical exploration of the sella for every patient with pituitary Cushing syndrome regardless of tomographic findings. Another decade of experience may be required to clearly establish that removal of such microadenomas can be done safely with prolonged remission of Cushing syndrome and preservation of normal pituitary function. However, the short-term results make it apparent that at least for the next decade pituitary surgical therapy has replaced total adrenalectomy as the primary treatment for adults with pituitary Cushing syndrome.

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Anaerobic Infections and Metronidazole

WITH NEWER MICROBIOLOGICAL TECHNIQUES, anaerobic infections are now recognized as a substantial hospital problem. These include particularly postsurgical, posttraumatic, female pelvic and pleuropulmonary infections; and anaerobes are a common component in abscess formation. In cases of sustained anaerobic bacteremia, mortality approaches 50 percent.

Currently available antibiotics against anaerobes have gaps in their spectrum of activity, most notably against Bacteroides species or major toxicity. Bacteroides species make up 10 percent of all bacteremias recognized in hospital.

Metronidazole has a broad spectrum of antimicrobial activity and its utility against amebic and trichomonal infections is well known. It also has rapid irreversible bactericidal action *in vitro* against anaerobes, including Bacteroides. In man, it penetrates well from the blood into body fluids

and appears to concentrate selectively in abscesses. It does not appear to antagonize other antibiotics.

It has been shown effective in treatment of patients with anaerobic sepsis or endocarditis, meningitis and brain abscess, posthysterectomy and postpartum pelvic infections, lung abscess or empyema, including patients who failed to respond to other antibiotics. In these cases, bactericidal blood concentrations correlate with successful outcome. It has also been effective in prophylaxis in bowel surgical procedures, appendectomy and gynecologic surgical operations.

Its use in antianaerobe therapy has been considered experimental in the United States in the absence of licensing for this indication. It has been available for oral administration only, but is absorbed after rectal administration and an intravenously given preparation is under study, which would allow therapy of seriously ill patients.

Side effects are minimal and infrequent, and include gastrointestinal disturbances at high doses, transient leukopenia and sensory neuropathy, headache and vestibular symptoms. Mutagenesis has been shown in bacteria but is of uncertain relevance, particularly because certain intracellular conditions correlated with this effect in bacteria have not been shown in humans. Carcinogenicity occurs in some rodents, but this is of uncertain significance since the doses and duration used in these experiments bear no relation to that used in human therapy.

Studies here and abroad indicate that this agent, at present undergoing further trials and possibly available in the future for general use in antianaerobe therapy in the United States, represents a major therapeutic advance—particularly against Bacteroides.

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Hepatitis B Immune Globulin in the Prevention of Hepatitis B

HEPATITIS B is a common infection reaching epidemic proportions in some populations. Previously referred to as "serum hepatitis," hepatitis due to the B virus is now known to be transmitted not only by parenteral routes but also by close physical contact and exposure of mucus membranes to the virus. Hepatitis B is easily diagnosed by showing the presence in serum of hepatitis B surface antigen (HB_sAg) or by a rising titer of antibody against the surface antigen (anti-HB_s). Recently, a preparation of hepatitis B immune serum globulin (HBIG) has become available.

HBIG can cost more than $150 per injection and two doses, approximately 30 days apart, are recommended. For comparison, ordinary gamma globulin (immune serum globulin, ISG), which may contain appreciable titers of anti-HB_s, costs less than $10.

HBIG is prepared from plasma in a manner similar to common ISG except that the donor source of plasma is high in titer of anti-HB_s. Both preparations are safe, neither transmits hepatitis, and side effects from intramuscular administration are low. HBIG has been shown in several controlled trials to reduce the likelihood of clinical illness and seroconversion due to hepatitis B. One large study of needle puncture exposure reported a 1.4 percent incidence of clinical hepatitis and a 5.6 percent seroconversion (anti-HB_s) in subjects given HBIG. This was in contrast to a 5.9 percent incidence of clinical hepatitis and a 20.7 percent seroconversion of subjects receiving immune serum globulin containing uncommonly *low* levels of anti-HB_sAg.

The United States Public Health Service Advisory Committee on Immunization Practices recommends the use of HBIG for patients with a single exposure to blood containing hepatitis B virus. This contact can take several forms, including needle puncture, mucus membrane contact or open wound contamination. Other less well established indications for HBIG use include exposure to body fluids other than blood products (urine, saliva, stool and the like), close physical contact with carriers of HB_sAG, and constant environmental exposure such as occurs in hemodialysis units or custodial institutions for the mentally retarded.

The initial intramuscular dose of 0.05 to 0.07 ml per kg of body weight should be given as soon as possible after exposure (not more than 7 days) and is followed by a second injection 30 days later. Confirmation of the HB_sAg positivity of the donor is mandatory and showing the absence of anti-HB_s is desirable if testing will not unduly delay gamma globulin prophylaxis. Chronic contact such as occurs in spouses of chronic carriers is not a sufficient indication for HBIG administration. Detailed questioning of the circumstances surrounding the actual exposure is necessary since many